REMARKS

Claims 1-12 are pending in this application and stand rejected. Claim 1 has been amended, and Claim 7 has been canceled. Basis for these amendments can be found on page 10, paragraphs [**0048**]-[**0052**] of the present application as published, i.e. US 2006/0014808 A1. Applicants respectfully request reconsideration in view of the Amendments and Remarks herein.

Claims 1-12 were rejected under 35 U.S.C. §103(a) in view of Lahm et al. (WO01/070483) (sic). Applicants respectfully traverse this rejection.

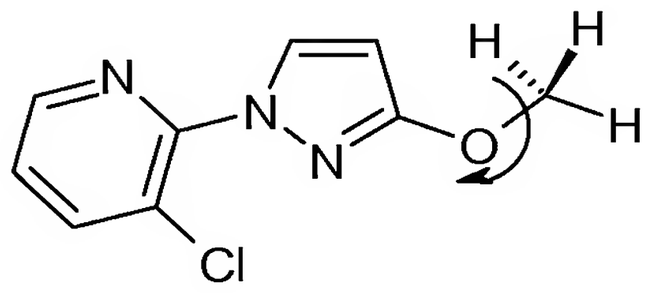
The publication number referred to by the Examiner in this rejection appears to contain a transcription error. WO01/070483 seems to correspond to both WO**01/070**671 and WO02/070**483**). However, upon review of the Examiner's remarks in the last paragraph on page 5 of the Office Action, Applicants believe that the reference to which the Examiner is referring is WO01/070671 given that the text "last paragraph on page 11, formula II on page 10 and formula III on page 11…" is more closely aligned with the description on the corresponding pages of WO01/070671 than WO01/070483.

Applicants point out that the majority of prepared compounds in Index Tables A-C and E-P from Lahm et al. discourage one skilled in the art from preparing compounds where J is the present pyrazole. For example Index Table A (disclosing 278 prepared compounds) contains compounds wherein J is phenyl motivating the skilled person to prepare compounds where J is phenyl. Index Tables B, C and K (containing a total of 160 prepared compounds) all teach compounds wherein J is a six-membered heterocyclic ring. Index Tables E, F, G, H, J, L, M, N and P (containing a total of 66 prepared compounds) all contain various five-membered heterocyles other than those in the present application.

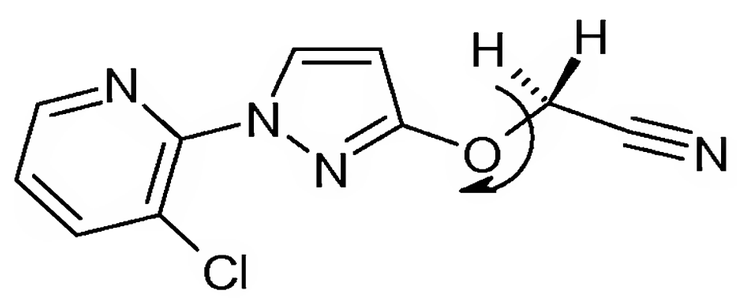
Possibly the most relevant Index Table from Lahm et al. is Index Table D. This Table lists compounds where J corresponds to the instant pyrazolecarboxamide. A variety of radicals for R^7(a) are listed in Index Table D, namely CF_3, CH_3, CH_2CH_3, CF_2CF_3, *c*-Pr, Br, Ph, C≡CH, H and CN. However, a significant improvement not suggested by the prepared compounds from Lahm et al. lies in the replacement of art R^7(a) with instant R^5. It is known by those of skill in the art that biological activity requires optimal interaction between the compound and its biological target such as an enzyme, receptor, or the like. Optimal interaction relies on whether the compound exhibits a complementary physiochemical profile, including the necessary electronic, steric, and conformational properties.

For example, a comparison of the R^7 substituent OCH_3 of Lahm et al. and the corresponding present R^5 substituent OCH_2CN (R^5 is OR^7 with R^7 being C_1 alkyl substituted with R^{11}, and R^{11} being cyano) illustrates why a skilled person would not have considered the present R^5 substituents. The steric, electronic and conformational property differences between the two groups are illustrated below.

Replacement of the OCH_3 group with the OCH_2CN group in effect replaces one small hydrogen atom with two larger, linearly-bonded non-hydrogen atoms, resulting in a significant increase in group size. This increase in size and shape has a severe conformational impact, as shown below in the comparison of the barriers to rotation of the two molecular fragments.

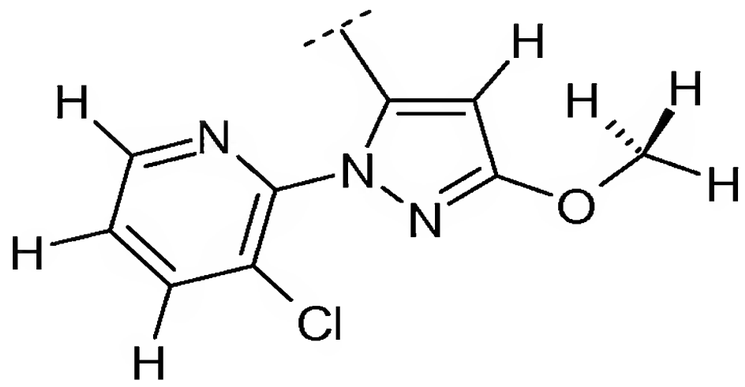


Lahm et al. OCH_3 fragment

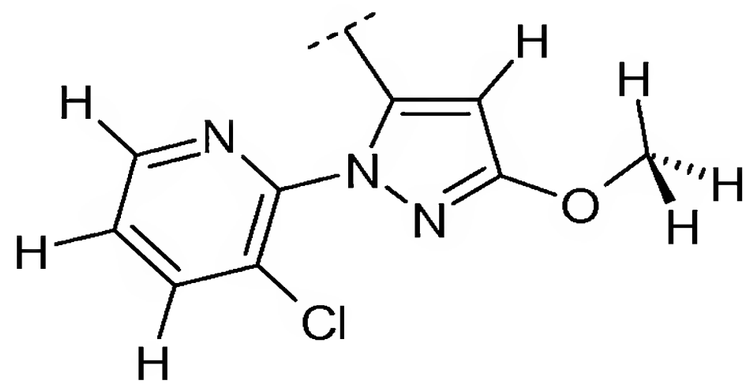


present OCH_2CN fragment

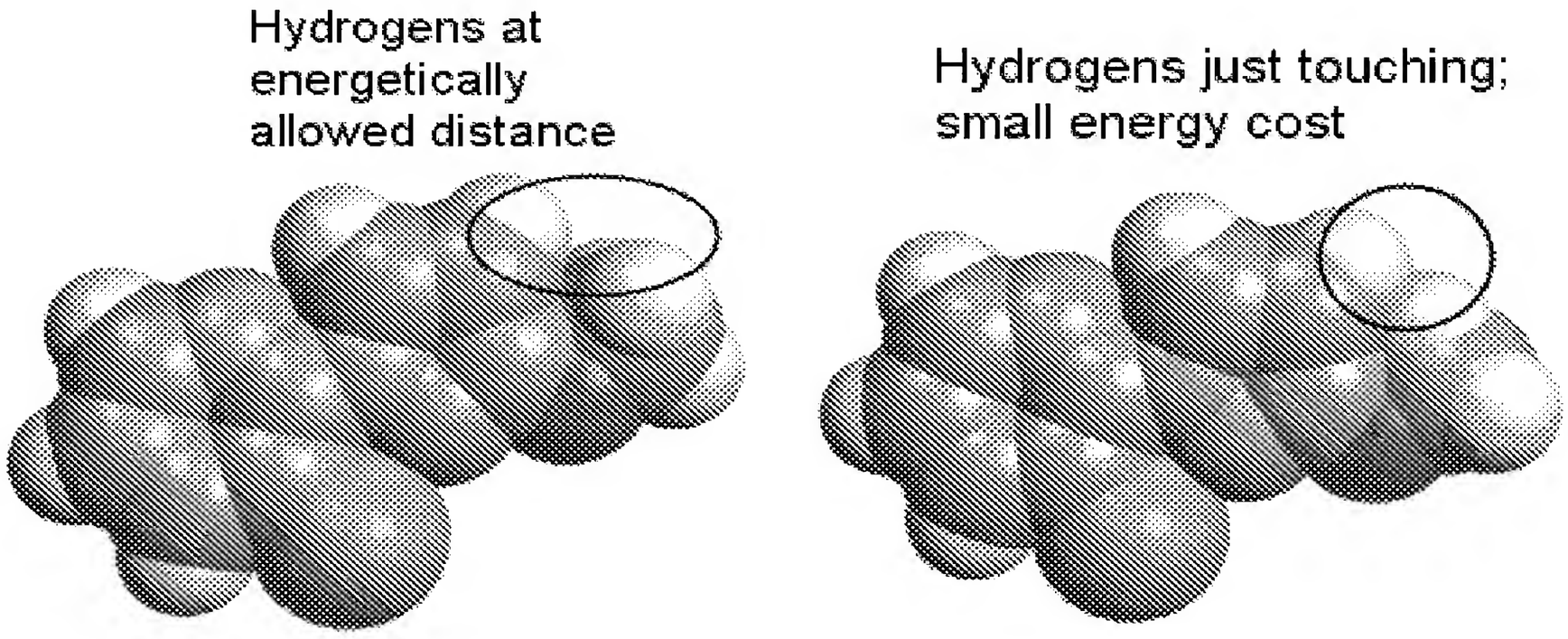
In the OCH_3 species, the small methyl group is conformationally free to move with little energetic cost. To demonstrate the different energetics between the two compounds, electronic and conformational analyses were performed by Argus Lab calculations with PM3 optimization. The rigid barrier to rotation, with the remainder of the fragment held fixed, was determined to be only 20.9 kJ/mol (5.0 kcal/mol), which permits free rotation at room temperature. Since the three hydrogen atoms are equivalent, there is no favored conformation around this bond. The "staggered" and "eclipsed" conformations are depicted below.



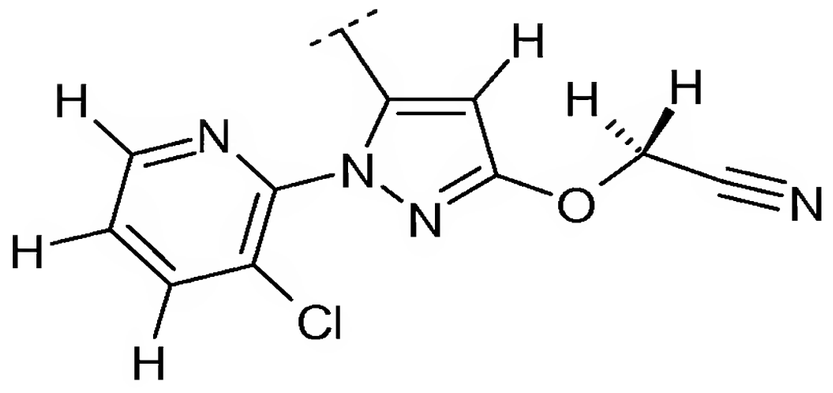
"staggered" OCH_3 species



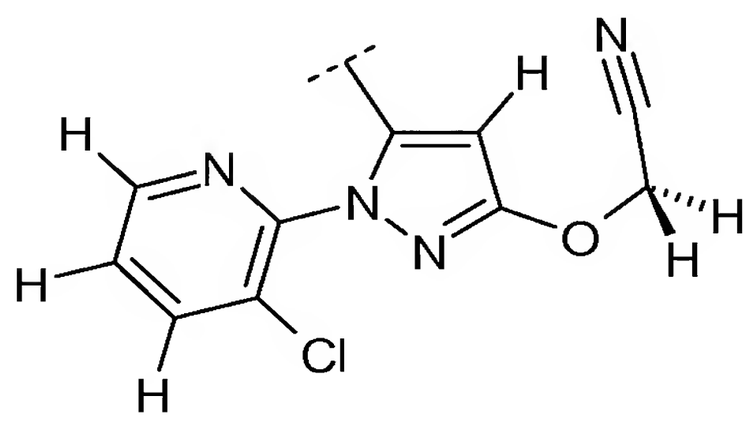
"eclipsed" OCH_3 species



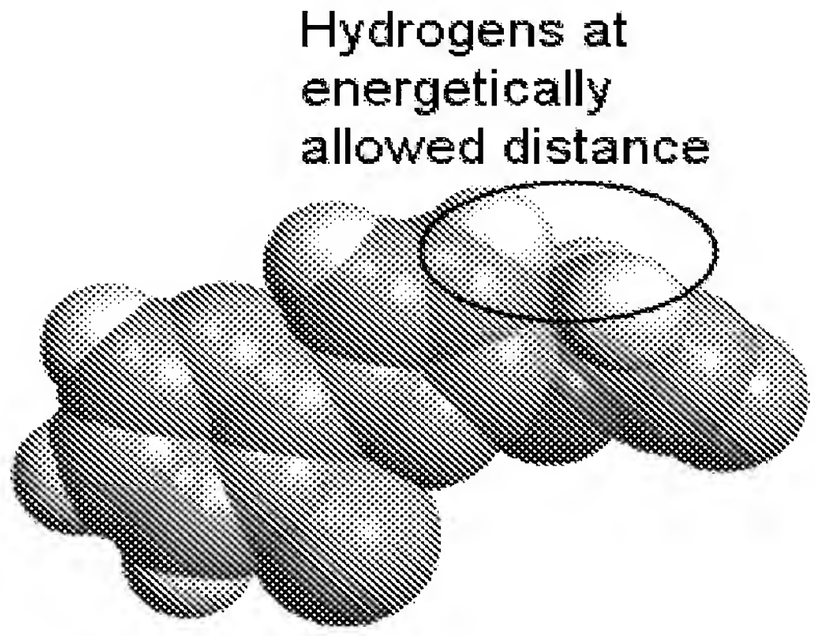
In the OCH_2CN species, the cyano substituent on the methylene group has the potential to clash with the pyrazole ring hydrogen atom. The rigid barrier to rotation is in excess of 335 kJ/mol (80 kcal/mol), far greater than the energy required to decompose the fragment entirely. In fact, a rigid rotation of this bond would require the impossibility of placing the pyrazole hydrogen inside the cyano nitrogen. Rotation around this bond is not allowed without further substantial changes to the conformation of this fragment, which will affect the fragment's ability to interact with other molecules such as its protein target. Additionally, the energetic cost associated with rotating the cyano group creates preferred and disfavored conformations of this moiety on the pyrazole that do not exist for the OCH_3 species.



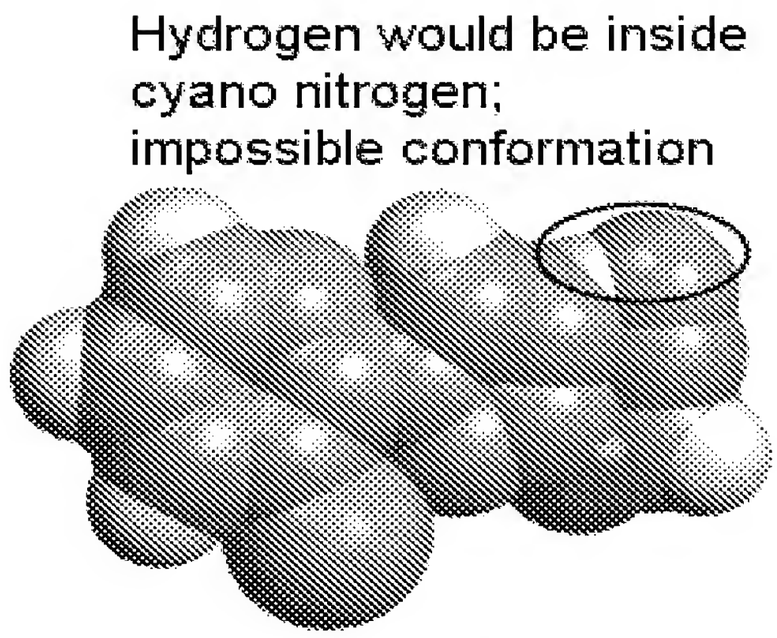
"staggered" OCH_2CN species



"eclipsed" OCH_2CN species

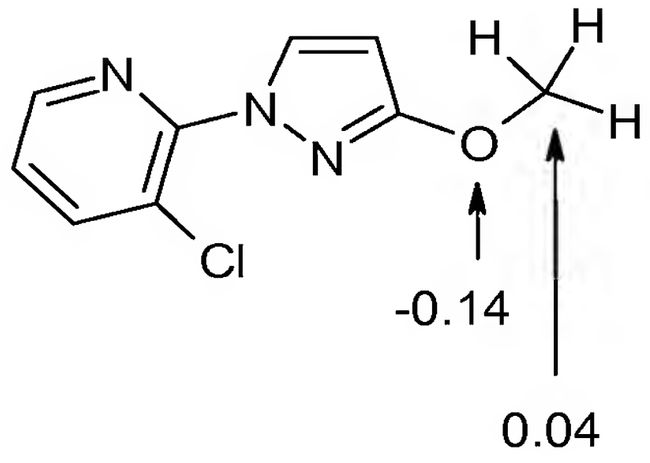


staggered form

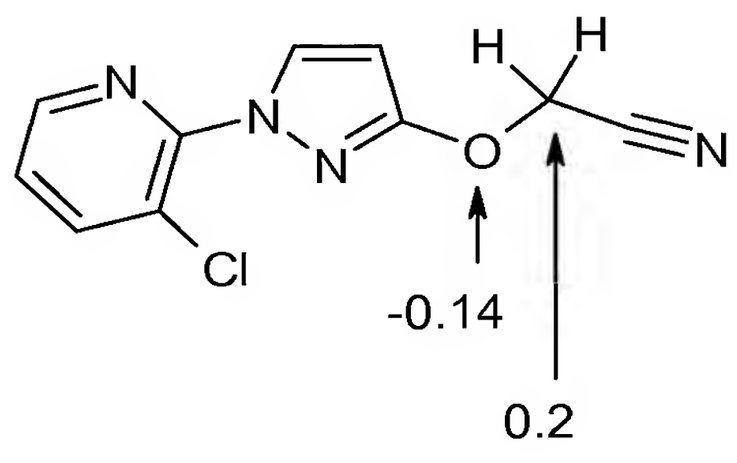


eclipsed form

Electronically, these two fragments also exhibit substantial differences. The electronegative nitrogen atom in the present OCH_2CN species provides an additional hydrogen bond acceptor to R^5. Furthermore, the electronic influence of the electron withdrawing nature of the nitrile group is felt on the adjacent carbon atom. The calculated atomic charges are shown below:



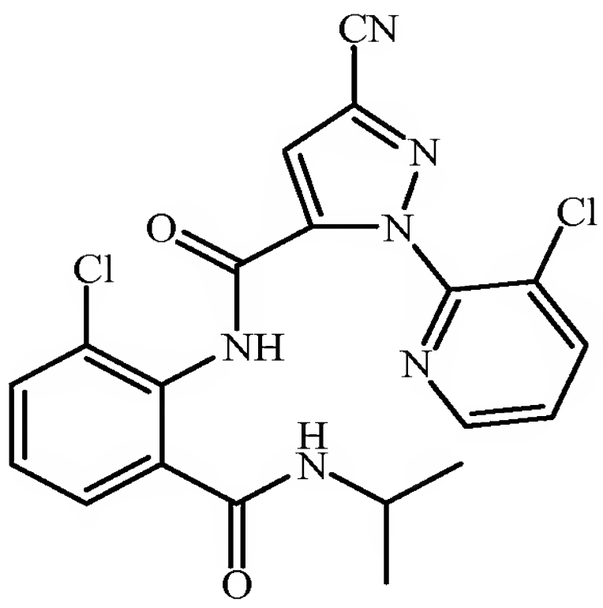
Lahm et al. OCH_3 fragment



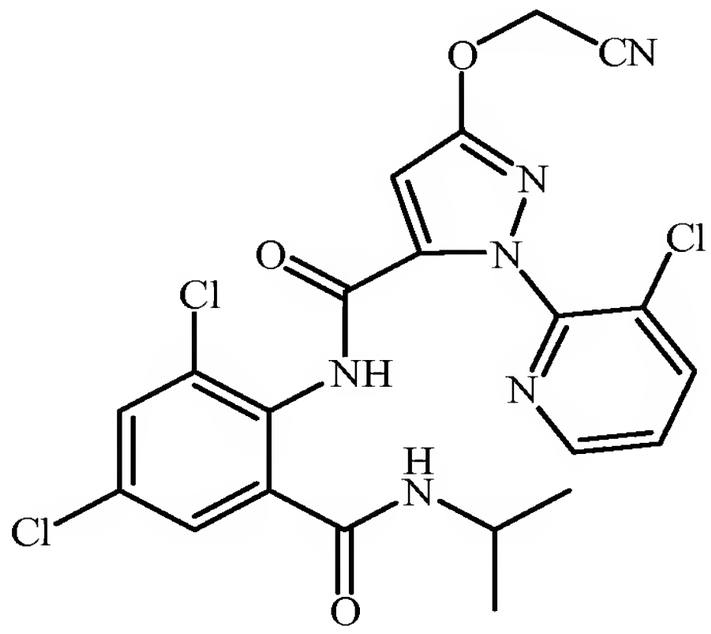
present OCH_2CN fragment

The charge distribution throughout the pyrazole nucleus is essentially the same in both species, and the electronic charge on both oxygen atoms is similar (-0.14). However, the OCH_3 fragment carbon atom is virtually neutral with a charge 0.04, while the OCH_2CN fragment's corresponding carbon atom has a significant positive charge of 0.2. These differences in electronic character would be expected to lead to significant differences in chemical reactivity and hydrogen bonding, which in turn lead to significant differences in biological activity. Increases in size and modifications in shape are known by those of skill in the art to influence receptor binding and thus biological response. Therefore Applicants maintain that such a modification would not have suggested to one of skill in the art compounds possessing biological activity.

Knowing that such seemingly small and inconsequential changes in substitution on the pyrazole ring can bring about significant differences in electronic character (and thus biological activity) can be applied to electron-withdrawing character. The skilled person, with knowledge that biological activity is observed for art D221 with R^7(a) being cyano (an electron-donating group) will not find it obvious that instant Compound 14 (from Index Table A) with R^5 being cyanomethyloxy (an electron-withdrawing group) to have better biological activity.

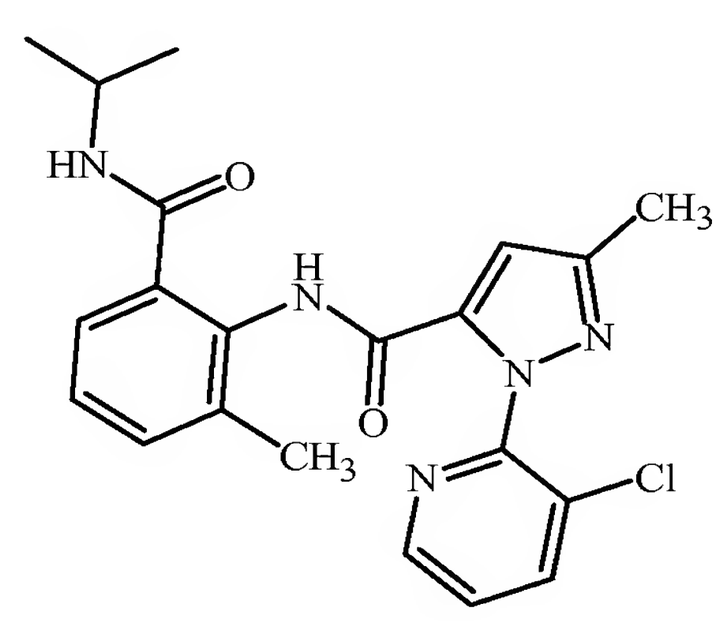


D221 (Lahm et al.)

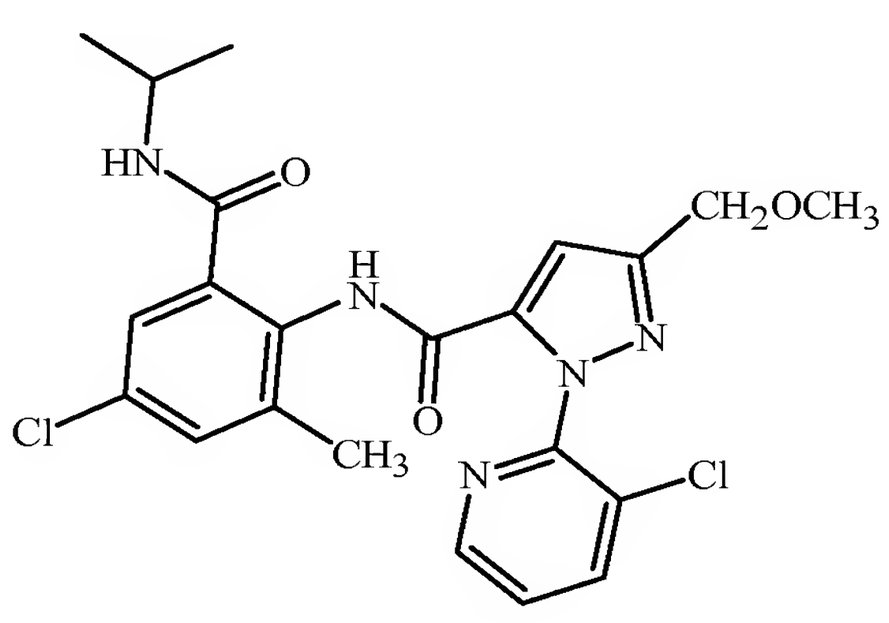


Compound 14 (present application)

Similar reasoning can also be applied to the hydrogen-bonding character of the pyrazole substituent. The skilled person with knowledge that biological activity is observed for art D242 with R^7(a) being methyl (a hydrogen-bonding group) will not find it obvious that a compound from the present invention (i.e. paragraph **[0130]** Table 2, the 4th compound in the left-hand column on page 26) with R^5 being methoxymethyl (a hydrogen-bonding group) to have better biological efficacy.



D242 (Lahm et al.)



4th compound in left-hand col. of page 26,
Table 2, paragraph **[0130]**
of US 2006/0014808A1
(present application)

Therefore Applicants maintain that there is nothing in Lahm et al. that would lead the skilled person to modify the R^5 substituent to arrive at the presently claimed compounds. Therefore, Applicants respectfully submit that the present claims are not suggested by the cited art.

Applicants also bring to the Examiner's attention the fact that at the time the present invention was made it was owned by the assignee of the Lahm et al. reference (WO01/070671), i.e. E. I. du Pont de Nemours and Company.

In view of the foregoing, allowance of the above-referenced application is respectfully requested.

Respectfully submitted,

/Linda D. Birch/

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